UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/560,124	04/28/2000	Ralph A. Nixon	50122/002003	3388

7590 03/25/2003

Kristina Bieker-Brady, Ph.D.
Clark & Elbing LLP
176 Federal Street
Boston, MA 02110

EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/25/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/560,124	NIXON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-31 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed January 13, 2003 (Paper No. 9) has been entered. Claims 16, 17, 22, 27, 30 and 35 have been amended. Claims 18, 23, 29, and 31 have been cancelled.

Accordingly, Claims 1-17, 19-22, 24-28, 30, and 32-35 remain pending in the instant application.

In the last Office Action (Paper No. 7, mailed 7/8/02), Claim 35 was examined with the invention of Group II, because it embraced the invention of Group II (the elected invention), although it also embraced the inventions of Groups I, III, and IV. Applicants were advised to cancel the non-elected subject matter from the claim (see the rejection under 35 U.S.C. 112, second paragraph). However, Claim 35 has been amended so that it is now directed exclusively to the invention of Group I (the screening method using a Tn65Dn mouse). Accordingly, Claim 35 is withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claims 1-15 and 32-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **with** traverse in Paper No. 6.

This application contains Claims 1-15 and 32-35 drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 16-31 are examined herein.

The following rejections are reiterated and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-20 and 22-25 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action of Paper No. 7 (mailed 7/8/02), because the specification, while being enabling for an *in vitro* method for identifying a candidate compound as a compound that may be useful for the treatment of Alzheimer's disease (AD), using cells expressing a recombinant nucleic acid encoding rab5, wherein the method is carried out *in vitro* (i.e., in cells in culture), does not reasonably provide enablement for an *in vivo* method for identifying a compound that may be useful for the treatment of AD, using a transgenic mouse expressing a transgene comprising a recombinant nucleic acid encoding rab5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for identifying a candidate compound as a compound that may be useful for the treatment of AD. The method involves providing a cell expressing a recombinant nucleic acid encoding rab5, contacting the cell with the candidate compound, and measuring the activity of the endocytic pathway. The claims cover *in vitro* and *in vivo* applications of the method. Claims 27-31 are exclusively directed to *in vivo* methods of using rab5 transgenic mice in identifying a candidate compound as a compound that may be useful for the treatment of AD.

At pages 4-9 of the response, Applicants argue that the production of transgenic animals is routine, that one can assess transgenic phenotype in multiple independent lines, that one can make transgene constructs to minimize position effects, that the experiments of Mullins et al. (1989) was successful because they generated transgenic mice, even though the mice did not have the desired phenotype to generate a model for hypertension. Applicants further argue that the variability in phenotype due to differences in genetic background is insignificant because the transgenic animals all had

a phenotypic alteration as compared to wild-type animals. Applicants assert that the skilled artisan could make rab5-overexpressing transgenic mouse that would produce endocytic pathway alterations. Applicants arguments all seem to be predicated on the belief that one of skill in the art could make a rab5 transgenic mouse and assess its phenotype and then use it in the claimed methods. The Examiner has already acknowledged that gene transfer methods are well-developed for mice (see page 4, paragraph 3 of the Office Action of Paper No. 7). However, the rejection is based on the argument that the phenotype of a transgenic animal is unpredictable, and therefore one cannot predict phenotype *a priori*. In order to teach how to use the rab5 transgenic mouse, the specification must teach the phenotype of the rab5 transgenic mouse. Furthermore, given the unpredictability of phenotype for reasons of record, one of skill in the art would not know *a priori* how to make a transgenic mouse having a specific desired phenotype. The specification does not teach the phenotype of a rab5 transgenic mouse.

Applicants conclude that none of the references cited supports the Office's assertion that the phenotype of a rab5 transgenic mouse would be unpredictable. However, ample reasons, supported by 6 references showing the state of the art, have been given to support the argument that the phenotype of a transgenic animal is unpredictable and therefore cannot be determined *a priori*. While the PTO bears the initial burden of providing reasons for doubting the objective truth of the statements made by Applicants as to the scope of enablement, when the PTO meets this burden, the burden shifts to applicant to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The Declaration of Dr. Ralph Nixon, filed January 13, 2003 (Paper No. 10) has been fully considered but is not found to be persuasive because the specification does not teach preparing rab5-overexpressing mice by HSV infection, thereby producing a transient overexpression of rab5. Rather the specification teaches using rab5 transgenic mice. Furthermore, since the specification does not teach the methodology employed in the experiments of the Declaration, the skilled artisan would not have the

benefit of the teachings supplied by the Declaration at the time of filing. It is well-established that a specification must provide an enabling disclosure at the time of filing. If a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while application is pending, by later publications or further experimentation which add to knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention; sufficiency under first paragraph of 35 U.S.C. 112 must be judged as of the filing date. If information to be found only in subsequent publications is needed for such enablement, it cannot be said that disclosure in application evidences a completed invention. *In re Glass*, 181 USPQ 31 (CCPA 1974).

In view of the limited guidance in the specification, the lack of working examples for rab5 transgenic mice, the unpredictability in the transgenic art with regard to phenotype, and the broad scope of the claims covering both *in vitro* and *in vivo* compound screening methods, one skilled in the art would have been required to engage in undue experimentation in order to practice the claimed method over the full scope.

Claims 27-31 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action of Paper No. 7 (mailed 7/8/02), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of using rab5 transgenic mice in identifying a candidate compound as a compound that may be useful for the treatment of AD. The claims are exclusively directed to *in vivo* methods of compound screening.

For the reasons discussed above, the specification fails to provide an enabling disclosure for methods of using a rab5 transgenic mice in compound screening.

Applicants argue that expression of a rab5 transgene in murine cells *in vitro* produces endosomal alterations and therefore it is reasonable to predict that a transgenic mouse expressing a recombinant rab5 transgene would display endocytic pathway alterations. However, given the demonstrated unpredictability in the transgenic art, a correlation between an in vitro effect and an in vivo effect would likewise be considered unpredictable. Furthermore, the Examiner has already acknowledged that the claims are enabled for carrying out the screening method *in vitro*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-31 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-31 remain indefinite in their recitation of "a compound that is useful for the treatment of Alzheimer's disease" because the assay does not provide a demonstration that the compound is actually useful for the treatment of Alzheimer's disease, but rather only provides an initial screening of compounds that may be useful for the treatment of Alzheimer's disease. Use of the claim language "a compound that may be useful for the treatment of Alzheimer's disease" is recommended.

At page 13 of the response, Applicants state that Claims 16-31 (and 35) now recite "a compound that may be useful. However, no such amendment has been made. The claims continue to recite "a compound that is useful for the treatment of Alzheimer's disease."

Conclusion

No claims are allowed.

Claims 21 and 26 would be allowable if amended to overcome the rejection under 35 U.S.C. 112, second paragraph.

This application contains Claims 1-15 and 32-35 drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER